Rejections under 35 U.S.C. § 112, First Paragraph

Claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96, and 115-147 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly is not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Citing the Wands factors, the Examiner alleges that undue experimentation would be required to make the pharmaceutical compositions and methods of the invention comprising DNA and a polynucleotide function enhancer because the specification allegedly does not demonstrate such a composition.

The Applicants respectfully traverse this rejection. The Examiner has not made convincing arguments that the present invention is not enabled with respect to **any** of the Wands factors. Furthermore, only two Wands factors, at most, are discussed for each aspect of the invention alleged to be non-enabled. When all the evidence is viewed in its totality, it is clear that those skilled in the art would accept the Applicants' assertion that the claimed invention could be practiced without undue experimentation.

Regarding the first Wands factor, the Examiner alleges that the immunogenicity of a specific antigen is unpredictable and that testing each potential antigen would involve undue experimentation. The Examiner has not given sufficient reasoning, and has not provided any evidence at all of this alleged undue experimentation.

> The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.

In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

The determination of antigen immunogenicity would not require undue experimentation. At the time of filing of the priority applications, the field of immunology was a well-developed field, procedures to determine the immungenicity of a protein were well known, procedures to screen for immunogenic proteins had a high success rate, and many immunogenic proteins suitable for the invention were known. The publication of Antibodies, a Laboratory Manual (E. Harlow and D. Lane, authors, Cold Spring Harbor Laboroatory, Cold Spring Harbor NY, 1988), four years before the earliest filing date of a priority application of the present application, is proof that the field of immunology field was well-developed at the priority date. This laboratory manual gives guidance on immunizing animals (pages 92-115), sampling serum (pages 116-123), and testing the serum for antibodies specific to the antigen (pages 555-589). At the time of filing, it was known that "simple injections of many foreign molecules, viruses, or cells elicit a strong antibody response in laboratory animals" (Harlow, page 55, lines 17-18), therefore it was expected that most screenings would yield immunogenic proteins and many immunogenic proteins were known. The determination of antigen immunogenicity, therefore, did not require undue experimentation at the priority date of the present application. If the Examiner maintains

that determining the antigenicity of an antigen would involve undue experimentation, he is requested to provide an affidavit under 37 C.F.R. § 1.104(d)(2).

Regarding the second Wands factor, the Examiner alleges that there is only prophetic guidance and no examples of the claimed invention in the specification.

> The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). The specification contains abundant working examples of pharmaceutical compositions comprising DNA vectors designed to raise an immune response to many encoded antigens. In particular, the specification contains several working examples of DNA pharmaceutical compositions that raised an effective immune response in a mouse. Example 3 (specification, pages 42-48) teaches a working example of a DNA vaccine against the HIV protein gp160 that successfully raised a specific immune response in a mouse. Example 28 (specification, pages 55-60) teaches a working example of a DNA vaccine against a T lymphoma antigen, CD4, that successfully eliminated transfected tumors in mouse. Example 29 (specification, pages 56-57) teaches a working example of a DNA vaccine against human GA733 colon cancer antigen that successfully eliminated transfected tumors in mice. Example 30 (specification, pages 57-58) teaches a working example of a DNA vaccine against the human neu oncogene that successfully eliminated transfected tumors in a mouse.

Although these examples teach the effectiveness of a DNA pharmaceutical composition without the polynucleotide function enhancer of the present invention, a working

example exactly teaching the invention is not required. It would have been well within the abilities of the skilled artisan to take the teachings of these working examples, add the disclosure of the formulation of the DNA pharmaceutical composition with the model polynucleotide function enhancer, bupivacaine (specification, page 28, line 20 - page 29, line 10), and make the pharmaceutical composition, method of immunizing and method of introducing DNA of the invention. Such an adaption of the given working example would not require undue experimentation since the necessary information is taught in the specification.

Regarding the third Wands factor, the Examiner alleges that the nature of the invention is complex by citing passages from Cho et al. to characterize the delivery of DNA into an animal as an allegedly "new and developing art" (Official Action of August 11, 2000, page 3, line 16). However, Cho et al. does not characterize the field of DNA delivery as highly unpredictable. Cho et al. summarizes that "the most challenging aspects of macromolecular therapeutics will be **optimizing** the delivery of high molecular weight drugs to their target sites within cells and tissue" (Cho, page 157, column 1, lines 18-21, emphasis added), and therefore teaches that the art of macromolecular delivery is well-established and merely becoming more refined. Cho et al., while discussing the different considerations for macromolecular therapeutics vs. small-molecule therapeutics, focuses primarily on the delivery of exogenous proteins to cells and tissues of the animal in therapeutic amounts and **never** suggests that DNA delivery requires a great deal of experimentation. On the contrary, Cho et al. discloses several popular protocols for the delivery of genes into the cells: complexing with polycations, absorbing into cationic liposomes, and/or uptake promoting

proteins (Cho, page 156, column 2, lines 6-12). Cho et al. clearly teaches that the delivery of polynucleotides is an accomplished and routine fact, therefore not requiring undue experimentation.

Regarding the fourth Wands factor, the Examiner alleges that, at the time of filing of the present application, the prior art was teaching that it was unknown if DNA vaccines would be effective. The Examiner further alleges that the field of DNA immunization is unpredictable in general, even today. Applicants respectfully urge that the Examiner is mistaken in this regard and the evidence relied upon is incomplete. The Examiner has not cited references to support this contention. Respectfully, the invention is not a DNA vaccine, but a pharmaceutical composition, a method for immunizing an individual, and a method for introducing DNA into the cells of an individual. The prior art at the time of filing and subsequent references contain many references that teach and provide evidence that pharmaceutical compositions comprising a DNA molecule that encodes an antigen are very likely to be successfully expressed and raise a specific immune response. Applicants provide herewith a bibliography of references downloaded from the DNA vaccine website, www.dnavaccine.com, which demonstrates the extensive body of research reporting the operability of various forms of DNA vaccines and other immunizations. In addition, provided herewith is the review article, Chattergoon et al. (1997, FASEB 11(10):753-763), which reports the development of the field of DNA vaccines. Finally, provided herewith is an article which was published in Scientific American (Weiner and Kennedy, 1999, Sci. Am. 281(1):50-57) which provides further review of the developments of DNA vaccines. Clearly, the skilled artisan would have appreciated that a pharmaceutical composition comprising a

DNA molecule encoding an antigen was very likely to be effective in transforming animals cells, expressing the antigen in the cells, and raising an immune response to the antigen. If the Examiner maintains that the prior art the time of filing taught that it was unknown if pharmaceutical compositions and methods of the invention would be effective, he is requested to provide an affidavit under 37 C.F.R. § 1.104(d)(2).

Regarding the fifth Wands factor, the Examiner alleges that those of skill in the art have taught the unpredictability of DNA vaccines, and has cited three references as evidence of his assertion. The first reference alleged to teach unpredictablity is Rabinovich et al. The passage of Rabinovich et al. cited by the Examiner addresses the development of subunit vaccines, however the present invention is **not** a subunit vaccine. The teachings of Rabinovich et al. would suggest to one skilled in the art that the claimed invention could be made without undue experimentation. Rabinovich et al. teaches that, in animal models, nucleic acid vaccines "stimulate persistent humoral and cell-mediated immune responses" and protect animals from lethal virus challenge (page 1403, column 2, second paragraph). Therefore, Rabinovich et al. teaches the effectiveness of DNA pharmaceutical compositions in not only raising an immune response, but also creating a protective effect. If safety issues exist, the assessment of these are not the duty of the Patent and Trademark Office, but the duty of the Food and Drug Administration.

The Examiner cites Webster et al. as evidence of unpredictability in that "the ultimate vector for use in DNA immunization . . . has not yet been perfected" (Official Action page 4, lines 13-15). That the **ultimate** vector of DNA immunization has not been perfected is hardly a reason to assert that a DNA pharmaceutical composition cannot be made without

undue experimentation. On the contrary, Webster et al. discloses many genes in vectors that have been successfully introduced into mammals in vectors, where they are expressed and an immune response is raised against the expressed proteins (see Webster et al., Table 1, page 278, for example). Webster et al. therefore teaches that there are vectors successfully being used to generate an immune response against encoded proteins. From Webster et al., it is clear that the use of vectors to raise an immune response *in animal* is well known and accepted in the art, and that one of skill in the art could make such a vector without undue experimentation.

The Examiner cites Piscitelli et al. as teaching unpredictability in that those of skill in the art are still evaluating the use of DNA to produce an HIV immunization. Respectfully, Piscitelli et al. does not address DNA AIDS immunizations at all, but only AIDS vaccines in general. Piscitelli et al. never suggests that there are any difficulties raising an immune response to HIV antigens. In fact, as the difficulties associated with HIV vaccine development are discussed at length in Piscitelli et al. (page 70, column 1, first paragraph), it is remarkable that if a problem raising an immune response exists, it is not mentioned. Additionally, the fact that potential HIV vaccines are still being evaluated is hardly evidence that a DNA immunization to HIV cannot be produced. The disclosure that several dozen candidate HIV **vaccines** are being developed and evaluated (Piscitelli et al., page 68, column 2, last paragraph) strongly suggests that those of skill in the art think that an effective HIV DNA **immunization** already exists. Furthermore, Piscitelli et al. teach that a successful AIDS vaccine has been developed in the rhesus monkey (SIV vaccine) (page 70, column 1, last paragraph) and in the domestic cat (page 70, column 2, paragraph 4). Clearly, animals

can be effectively immunized with AIDS antigens, therefore it is very likely that humans can also be effectively immunized with AIDS antigens without undue experimentation.

Finally, the analysis of the Wands factors has not been properly performed, and therefore no conclusion on nonenablement can be made from it.

> It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole.

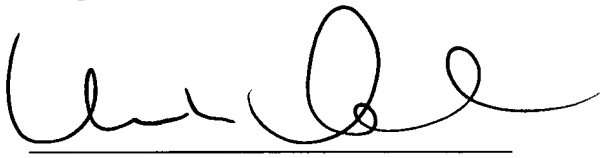
In re Wands, 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407 (Fed. Cir. 1988). The Examiner alleges that there is undue experimentation involved with several aspects of the present invention, but does not perform a proper analysis of the Wands factors for each aspect individually. This improper analysis leads to insufficient evidence on which to allege undue experimentation for any one aspect of the invention. For example, the Examiner alleges evidence of undue experimentation regarding the immunogenicity of the antigen in Parts a and e of the Wands analysis. The Examiner alleges evidence of undue experimentation for the aspect of the delivery of the DNA vector to the cell in Part e. The Examiner alleges evidence of undue experimentation regarding the vector used in the DNA pharmaceutical composition in Part e of the Wands analysis. The Examiner alleges evidence of undue experimentation regarding the HIV immunization also in Part e of the Wands analysis. At best, there are only two Wands factors discussed for any one aspect of the invention, and the other Wands factors have not been addressed. Therefore, the evidence of undue experimentation is insufficient for any one aspect of the invention for which non-enablement is alleged.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

Conclusion

For the foregoing reasons, Applicants submit that the present claims meet all the requirements for patentability. The Examiner is respectfully requested to allow all the present claims. If the Examiner is of a contrary view, it is requested that he contact the undersigned at (215) 564-8372.

Respectfully submitted,



Mark DeLuca
Registration No. **33,229**

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Woodcock Washburn Kurtz
Mackiewicz and Norris LLP
One Liberty Place - 46th Floor,
Philadelphia, PA 19103,
(215) 557-5948

Attachment: Bibliography
Chattergoon et al., FASEB Article
Weiner and Kennedy, Scientific American Article